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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,017	03/02/2004	Maik Obendorf	2877	1212

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,017	OBENDORF ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,12,13,19-22,26,27 and 31* is/are pending in the application.

4a) Of the above claim(s) *12,13,19-22,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8 and 31* is/are rejected.

7)☐ Claim(s) *5, 8* is/are objected to.

8)☒ Claim(s) *3-8,12,13,19-22,26,27 and 31* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 9/23/05 has been entered in full. Claims 3, 5, 6 and 8 are amended. Claims 1, 2, 9, 14-18, 23-25 and 28-30 are canceled. New claim 31 is added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 3-8 and 31 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (3/31/05).

The objection to the specification at pg 3 for lacking a sequence identifier for the sequences in Figure 3 is *withdrawn* in view of Applicants' amendments to the Brief Description of the Figures in the specification that identify the nucleic acid sequence in Figure 3 as SEQ ID NO: 1 and the amino acid sequence of Figure 3 as SEQ ID NO: 2. Please see new objections to the specification, below.

The objection to the specification at pg 3 for lacking a sequence identifier for the sequence "LXXLL" on pg 8, line 23 of the specification, is withdrawn in view of Applicants' persuasive arguments at pg 17-18 of the 9/23/05 response. The Examiner agrees with Applicants' position that the term LXXLL-motives "is a "higher level" term" that does not require a sequence submission.

The objection to claims 1 and 17 at pg 3-4 is *withdrawn* in view of Applicants' cancellation of the claims.

The objection to claims 3, 5 and 6 at pg 3-4 is *withdrawn* in view of Applicants' amendments to the claims.

All rejections of claims 1, 2, 9, 14-18, 23-25 and 28-30 are *withdrawn* in view of Applicants' cancellation of the claims.

The rejection of claims 3-8 under 35 U.S.C. § 112, first paragraph at pg 4-9 for lack of enablement is *withdrawn* in view of Applicants' amendments to the

claims. However, upon further consideration of the claims, a new rejection under U.S.C. § 112, first paragraph for lack of enablement is set forth below.

The rejection of claims 3-8 under 35 U.S.C. § 112, first paragraph at pg 9-12 for lacking written description is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 3 under 35 U.S.C § 112, second paragraph, at pg 12-13 for missing essential method steps is *withdrawn* in view of Applicants' amendments to the claim.

The rejections of claims 3-8 under 35 U.S.C. § 102(a) at pg 14-15 as being anticipated by Araya et al (2003) is *withdrawn* in view of Applicants' amendments to the claims.

Please see new claim objections and rejections, and new objections to the specification, below.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is noted that the instant application claims priority to the U.S. Provisional Application 60/465692, filed April 25, 2003. However, said provisional application is written in German. Priority to the filing date of said document will not be given unless Applicant provides an English translation. This was set forth in the 3/31/05 Office Action. Applicants' 9/23/05 response does not address this issue.

Specification

The disclosure is objected to because of the following informalities:

1) Because Applicants have not provided an English translation of Provisional Application 60/465692, priority to the filing date of the provisional application is not granted to the instant application, and the specification of the instant application is objected to for including this Provisional Application in the section, "CROSS-REFERENCE TO RELATED APPLICATIONS".

2) The content at the start of the specification is not in correct order. As provided in 37 CFR 1.77(b), the first two sections of the specification of a utility application should be (a) TITLE OF THE INVENTION and (b) CROSS-REFERENCE TO RELATED APPLICATIONS. Each of these items should appear in upper case, without underlining or bold type, as a section heading. The title of the invention should be placed at the top of the first page of the specification unless the title is provided in an application data sheet (See 37 CFR 1.72(a) and MPEP § 606). The section CROSS REFERENCE TO RELATED APPLICATIONS should immediately follow the title as the first line of the specification. Currently, the TITLE is near the bottom of the first page, and there is extraneous text before ("BE IT KNOWN...") and after the title ("of which the following...").

3) The specification contains two different descriptions of Figure 5a, one at page 21, lines 11-23 and another at page 22, lines 8-13. It is unclear how these relate to each other.

4) The specification is inconsistent as to the length of the androgen receptor fragment used in the yeast two-hybrid assays. Example 1, pages 18-19 state "the longest fragment (AR2) coded for the C-terminus (AS 325-918)..." However, the description of Figure 1 on page 16 states "(AR2) is designated as AS: 325-919". The description of Figure 3 on pages 19-20 states "...binds to the androgen receptor section AS 325 to AS 919". Furthermore, the specification indicates that the sequence of the androgen receptor is Genbank AAA51775. The Examiner has made this Genbank sequence of record on the PTO-892

attached to this Office Action. However, the androgen receptor sequence shown in AAA51775 is 918 amino acids in length. The claims refer a fragment comprising "amino acids 325-919". Furthermore, if the correct length is "918", then Figure 1 must also be corrected because it shows "AS: 325-919".

5) The specification is inconsistent as to the length of the Ewing Sarcoma protein fragment that binds the androgen receptor. The Brief Description of Figure 2 on page 16 states the androgen receptor binding domain is AS 219-656. However, page 19, line 20, states that this region is AS 319-656.

6) The disclosure is not in sequence compliance for the following reasons: On page 18, the specification refers to "the cDNA for the human androgen receptor (Genbank AAA51775)." Applicants are referred to MPEP 2422.03 "The Requirements for a Sequence Listing and Sequence Identifiers": In those instances in which prior art sequences are only referred to in a given application by name and a publication or accession reference, they need not be included as part of the "Sequence Listing," unless an examiner considers the referred-to sequence to be "essential material," [emphasis added]. In the instant case, the the androgen receptor sequence is "essential material" because the claims refer to amino acids 325-919 of a human androgen receptor. Furthermore, Accession numbers and the sequences associated with these numbers are subject to change and/or revisions. Therefore, the sequence of the androgen receptor of AAA51775 is considered essential material for this application and Applicants must include this sequence as part of the "Sequence Listing" in order for the application to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Appropriate correction is required.

Claim Objections

1) Claims 5 and 8 is objected to for containing the word "hepatocyes", which appears to be a misspelling of the word "hepatocytes", which is spelled correctly on pg 9, line 17 of the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

Claims 3-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening comprising a full-length Ewing sarcoma protein of SEQ ID NO: 2 and a full-length human androgen receptor, does not reasonably provide enablement for methods of screening with fragments of said proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Each of the claims encompasses a method of screening for compounds that affect the interaction between a fragment of EWS comprising amino acids 319-656 and a fragment of AR comprising amino acids 325-919, when each fragment is expressed in a cell. With respect to claim 3 (and dependent claims 4, 5, and 31), the goal of the claimed method is to identify a compound that alters binding between said fragments. With respect to claims 6-8, the goal of the claimed methods is to identify a compound that alters transcriptional activation by the androgen receptor. However, although the specification enables methods of

screening for modulators of the interaction between full-length EWS and full-length AR, the specification does not provide enablement for fragments of EWS or AR. While Applicants have shown that these fragments interact in a yeast 2-hybrid assay, Applicants have not shown that these fragments are capable of activating transcription via the androgen receptor. First, the relevant art teaches that amino acids 141-338 of the androgen receptor are need for full ligand-inducible transcriptional activity (see pg 176 of Heinlein, et al. Endocrine Reviews. 23(2): 175-200). Second, even with a full-length AR, it is unpredictable whether amino acids 319-656 of EWS are sufficient to act as a coactivator of AR-mediated transcription. While this fragment is sufficient for binding, it is unpredictable whether or not it is sufficient to act as a coactivator. Residues 1-318 represent almost half of the entire EWS protein and deletion of this much of the protein will have an unpredictable effect on the ability of the EWS protein to act as a coactivator of AR-mediated transcription.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495; cited in the 3/31/05 Office Action]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of

ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427; cited in the 3/31/05 Office Action].

Furthermore, while the method would identify test compounds that alter binding between the fragments of EWS and AR, these test compounds may or may not act differently in context of the full-length proteins, which contain significantly more amino acids than the fragments, and each residue may contributing to the three-dimensional structure of the protein that influences binding and transcription-activating properties of the complex.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether or not the method of the present invention could be used to determine the hormonal effect of substances using the recited fragments of EWS and/or AR. There are no examples of AR-mediated transcription activity using fragments of EWS and AR. Thus the specification fails to teach the skilled artisan how to use the method for screening without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the method could be used for screening, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 3-8 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 6 are indefinite because it refers to amino acids 325-919 of human androgen receptor it is unclear what sequence is being referred to. This is unclear for two reasons: 1) androgen receptors are polymorphic in length; therefore it is unclear in these claims what human androgen receptor sequence is being referred to; and 2) the specification refers in Example 1 to the androgen receptor of Genbank AAA51775; however the sequence of this receptor is 918 amino acids in length.

Claims 3-6 and 31 are indefinite because it is unclear what is meant by "hormonal effect".

Claim 6 is indefinite because it is unclear how cells are "transfixed" with a reporter construct. With respect to this issue, the claim would be rendered definite if amended, for example, to replace "transfixed" with "transfected" (as taught on pg 21, line 1 of the specification).

Claim 31 is indefinite because the elements recited in the claims do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Bridget C. Bunner

BRIDGET BUNNER
PATENT EXAMINER